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Natural history of cervical epithelial abnormalities in patients with vulval warts

A colposcopic study

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SUMMARY The natural history of intraepithelial abnormalities of the cervix associated with human papillomavirus infection was investigated in a prospective study of 50 women with vulval warts, of whom 28 had colposcopic evidence of a cervical epithelial abnormality and 22 a normal cervix. Of the 28 with a cervical abnormality, 26 were re-examined by colposcopy after three months; the epithelial abnormality had persisted in 23 women. Nineteen women who had initially shown abnormality by colposcopy were re-examined six months after their first attendance; the epithelial abnormality had persisted in 14 women.

Of the 22 women who initially had a normal cervix, 19 were re-examined after three months; the cervix remained normal in 18, but an epithelial abnormality had developed in one. Fourteen women who initially had a normal cervix were re-examined six months after their first attendance; the cervix was still normal in 11, but an epithelial abnormality had developed in three.

Colposcopically directed biopsy specimens were obtained from 21 women who showed an epithelial abnormality; of these, evidence of wart virus infection was present in four, cervical intraepithelial neoplasia in two, both conditions in 13, and no abnormality in two. It is concluded that lesions of the cervix associated with wart virus infection show little evidence of short term regression.

Introduction

In a preliminary communication[1] we reported a high prevalence of cervical epithelial abnormalities in women with vulval warts presenting at a clinic for sexually transmitted diseases (STD). There was colposcopic evidence of an epithelial abnormality in 28 of 50 patients examined, nine having abnormal epithelium consistent with a diagnosis of cervical intraepithelial neoplasia (CIN) with wart virus infection (WVI), 11 changes consistent with WVI as sole abnormality, and eight evidence of CIN as the sole abnormality. In the other 22 patients no cervical abnormality was detected. No biopsy specimens were taken from any of these patients, and arrangements were made to re-examine them three and six months after their first attendance to observe any changes in the colposcopic appearance of the cervix. Such changes would give useful information about the natural history of cervical epithelial abnormalities associated with human papillomavirus (HPV) infection.

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Patients and methods

The demographic data for the 50 patients studied have been given in an earlier report[1]; the average age of the group was 24 years, and details of their sexual history and microbiological findings showed them to be in no major way different from the usual clinic population. All 50 women were given an appointment for a further colposcopic examination at least three months after the first visit. At this attendance the patients who had initially been found to have no colposcopic evidence of an epithelial abnormality were examined for any changes consistent with a diagnosis of either WVI or CIN. Patients previously found to have an abnormal cervix

were re-examined to see whether the epithelial abnormality had regressed, persisted, or progressed.

As on the first visit, to reduce interference with the natural history of these lesions no biopsy specimens were taken unless there was evidence that the lesion was progressing or the patient would be unavailable for reassessment after a further three months. Each woman who had not undergone a biopsy was given another appointment at least six months after her initial visit. At the final visit, if an epithelial abnormality persisted, a colposcopically directed biopsy was performed and the patient received appropriate treatment.[2] If the cervix was found to be normal the patient was advised to have a further cervical smear in six months.

Biopsy material was fixed in formol sublimate, embedded in paraffin, and divided at three levels before staining with haematoxylin and eosin. Histological evidence of CIN was sought.[3] The principal change thought to be suggestive of WVI was the finding of koilocytotic atypia in the cells of the upper third of the epithelium; additional features were individual cell keratinisation, the presence of multinucleate cells, hyperkeratosis, and parakeratosis.

Results

In the original study group of 50 patients 28 had a cervical epithelial abnormality detected by colposcopy. Of these, two defaulted, so that 26 women were available for study after three months. The epithelial abnormality was found to have persisted in 23 cases (six of whom underwent biopsies at this visit), but in three the cervix was found to be normal. One further patient from this group defaulted after this visit, so that 19 patients who had originally had a colposcopic abnormality were available for study after six months. In 14 of these women the lesion persisted, and five were found to have a normal cervix.

At their first attendance 22 patients with vulval warts had a normal cervix by colposcopy. Of these, three defaulted, so that 19 were available for assessment after three months. Of these 19 patients, the cervix was found to be normal in 18, but an epithelial abnormality had developed in one patient. A further five patients from this group defaulted after this visit, so that 14 were available for study after six months. In these 14 women the cervix remained normal in 11, but three patients had developed epithelial abnormalities.

Althogether five patients had an epithelial abnormality at their first visit which regressed after six months. The colposcopic diagnosis of the abnormality had been WVI in four cases and CIN in

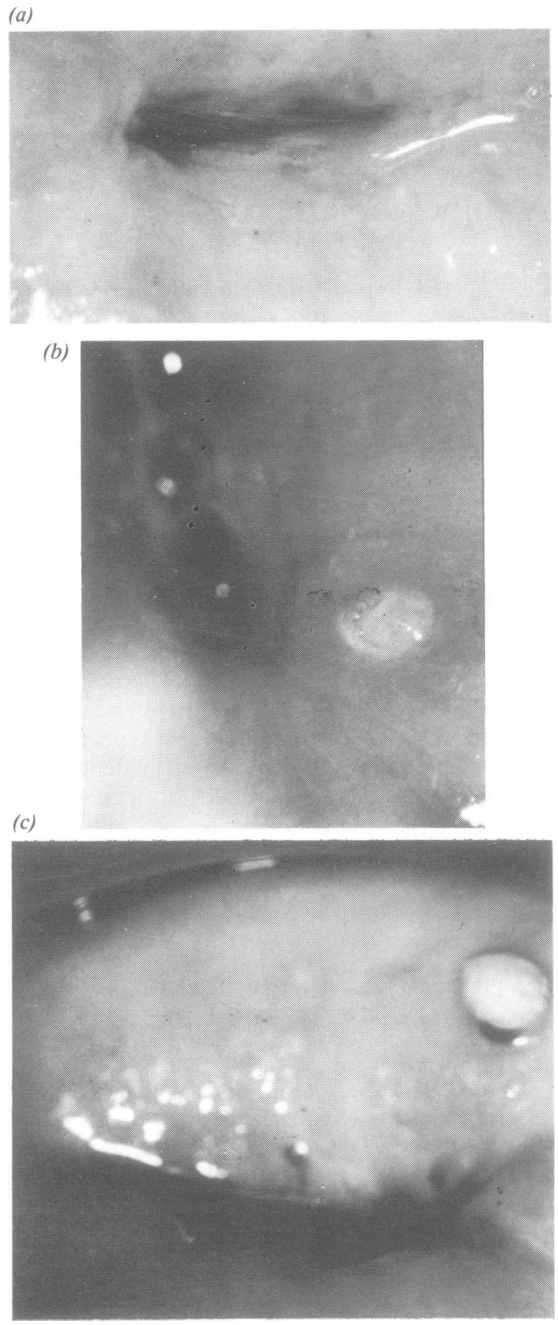

FIGURE *Colpophotographs of the cervix of a patient (a) at the first visit showing no evidence of any epithelial abnormality (× 6 magnification); (b) at the second visit (note the development of an epithelial abnormality to the right on the anterior lip) (× 10 magnification); and (c) at the third visit (note that the epithelial abnormality is now an exophytic condyloma) (× 6 magnification).*

one. Three patients developed epithelial abnormalities six months after their first attendance; the colposcopic diagnosis of these lesions was WVI as the sole abnormality in one case, CIN as the sole abnormality in another, and CIN with WVI in the third. Serial colpophotographs show that at her first visit one patient had a normal cervix, at her second visit an intermediate lesion suggestive of WVI, and at her final attendance an exophytic condyloma (figure). HPV antigen was found in biopsy specimens from this lesion using an immunohistochemical technique and an antiserum raised against an internal capsid antigen of HPV.

During the course of this investigation colposcopically directed biopsy specimens were obtained from the cervix in 21 women thought to have an epithelial abnormality. The histological reports on these specimens were: CIN with WVI in 13 cases, WVI as the sole abnormality in four, CIN as the sole abnormality in two; and no evidence of abnormality in two. The degree of intraepithelial neoplasia diagnosed by histology in the 15 cases reported were: CIN 1 in eight patients, CIN 1/2 in four, CIN 2 in two, and CIN 2/3 in one. No patient was found to have evidence of a CIN 3 lesion during the study. Seventeen biopsy specimens were examined from patients thought to have evidence of cervical wart virus infection by colposcopy, and histological evidence of a papillomavirus lesion was found in 13 (76·5%) of these.

Discussion

The confirmation of a colposcopic diagnosis of a cervical epithelial abnormality by histology in directed biopsy specimens from 19 of 21 women with vulval warts indicates that colposcopy is a valuable tool for the diagnosis of early intraepithelial abnormalities of the cervix associated with HPV infection. The correlation between the results of colposcopy and those of histology resembles that which we have obtained in a larger series of women presenting because of abnormal cytology reports; although it is not always possible to distinguish between WVI and CIN by colposcopy, those lesions most likely to be associated with HPV infection may be identified.[4] In our patients with vulval warts in the present study a colposcopic diagnosis of an epithelial abnormality associated with WVI was confirmed by histology in over 75% of cases.

The exact relationship between WVI and CIN is not known, but zur Hausen has recently proposed that HPV may act as a "promoter" in the aetiology of squamous cancer of the cervix.[5] The histological evidence of CIN in biopsy specimens from 15 of 50 women presenting with vulval condylomata acuminata suggests that such patients may be at high risk of developing carcinoma of the cervix. zur Hausen acknowledges that his hypothesis that herpes simplex virus infection or other "initiating" events may influence the action of HPV as "promoter" requires substantiation. Part of this may come from studies of the natural history of early epithelial abnormalities of the cervix associated with papillomavirus infection, as has been attempted on a small scale in the present investigation.

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